

# Evolution in Pancreas Transplantation Techniques: Simultaneous Kidney-Pancreas Transplantation Using Portal-Enteric Drainage Without Antilymphocyte Induction

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## Objective

To report initial experience with the combination of a novel technique of portal-enteric pancreas transplantation with newer immunosuppressive strategies that eliminate antilymphocyte induction therapy.

## Background

A new surgical technique of pancreas transplantation has been developed with portal venous delivery of insulin and enteric drainage of the exocrine secretions (portal-enteric). The introduction of potent immunosuppressive agents may allow simultaneous kidney and pancreas transplants (SKPT) to be performed without antilymphocyte induction.

## Methods

From September 1996 to November 1998, the authors performed 28 primary SKPTs with portal-enteric drainage and no antilymphocyte induction. All patients received triple immunosuppression with tacrolimus, mycophenolate mofetil, and steroids. The study group had a mean age of 38 years and a mean preoperative duration of diabetes of 25 years. Four patients (14%) had prior kidney transplants.

## Results

All patients had immediate renal allograft function. Actual patient, kidney, and pancreas graft survival rates were 86%, 82%, and 82%, respectively, after a mean follow-up of 12 months. Four patients died, three as a result of cardiac events unrelated to SKPT. Five kidney and five pancreas grafts were lost, including five deaths with function and three cases of chronic rejection. The mean length of stay and total charges for the initial hospital stay were 12.5 days and \$99,517. The mean number of readmissions was 2.9, and 10 patients (36%) had no readmissions. Six patients (21%) developed acute rejection, with five (18%) receiving antilymphocyte therapy. Seven patients (25%) underwent relaparotomy, including two (7%) for intraabdominal infection. Nine patients (32%) had major infections, including three (11%) with cytomegaloviral infection. Of the 24 surviving patients, 22 (92%) are both dialysis- and insulin-free.

## Conclusion

These preliminary results suggest that SKPT with portal-enteric drainage without antilymphocyte induction can be performed with excellent outcomes.

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The results of pancreas transplantation continue to improve as a result of refinements in surgical techniques and advances in immunosuppression. To date, most of the 10,000 pancreas transplants reported to the International

Pancreas Transplant Registry have been performed using the technique of systemic venous delivery of insulin and bladder drainage of the exocrine secretions (systemic-bladder).<sup>1</sup> Although systemic-bladder drainage is safe and effective, it results in peripheral hyperinsulinemia and is associated with unique metabolic and urologic complications.<sup>2,3</sup> Therefore, a resurgence of interest has occurred in primary enteric drainage of the exocrine secretions to avoid the complications of bladder drainage. The majority of pancreas transplants with enteric drainage are performed with systemic venous delivery of insulin (systemic-enteric).

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To improve the physiology of pancreas transplantation further and avoid the potential complications of systemic hyperinsulinemia (e.g., dyslipidemia and accelerated atherosclerosis), a new surgical technique was developed at our center with portal venous delivery of insulin and enteric drainage of the exocrine secretions (portal-enteric [PE]).<sup>4</sup> We have previously reported that patient and graft survival rates were similar with PE drainage compared with systemic-bladder drainage, but there was a marked reduction in bladder-related complications and a greater improvement in the lipoprotein composition with PE drainage.<sup>5,6</sup>

Most pancreas transplant centers initially use quadruple drug immunosuppression with antilymphocyte induction (ALI) because of a high incidence of rejection and the general belief that the pancreas is a highly immunogenic organ.<sup>7</sup> The evolution of surgical techniques has been in large part facilitated by the rapid changes in immunosuppressive therapy. Between 1989 and 1995, 94% of pancreas transplants were performed with systemic-bladder drainage and 88% with quadruple immunosuppression with ALI.<sup>1,7</sup> The addition of an antilymphocyte agent provided enhanced immunosuppression in the early posttransplant period, but it was associated with added costs and adverse reactions. With the recent commercial availability of potent immunosuppressive agents such as tacrolimus and mycophenolate mofetil (MMF), the need for routine ALI therapy after pancreas transplantation is in question.<sup>7</sup>

The purpose of this study was to evaluate an initial experience in simultaneous kidney and pancreas transplants (SKPT) combining the PE drainage technique and an immunosuppression regimen of tacrolimus, MMF, and steroids without ALI.

## MATERIALS AND METHODS

### Study Design

The pancreas transplantation program at the University of Tennessee, Memphis, began in 1989. The first transplant using PE drainage was performed in October 1990. Since 1989, we have performed 195 pancreas transplants, including 104 with PE drainage, 76 with systemic-bladder drainage, and 15 with systemic-enteric drainage. In the PE group, 80 patients underwent SKPT and the remaining 24 received solitary pancreas transplants (12 pancreas transplants alone, 12 pancreas transplants after a previous kidney transplant). From 1989 to 1994, immunosuppression consisted of quadruple therapy with OKT3 induction in combination with cyclosporine, prednisone, and azathioprine. In 1995, maintenance immunosuppression was switched from cyclosporine to tacrolimus-based therapy. In 1996, MMF replaced azathioprine in the quadruple-drug regimen. In September 1996, we began a pilot study of SKPT with an immunosuppression regimen of tacrolimus, MMF, and prednisone without ALI.

Since this time, our center has been involved in two

prospective studies comparing different techniques of pancreas transplantation. In 1997, we compared systemic-bladder with PE drainage. In 1998, we compared systemic-enteric with PE drainage.

Between September 1996 and November 1998, a total of 80 pancreas transplants were performed at our center, including 56 SKPTs. Of these SKPTs, 32 were performed with PE drainage, of which 4 were excluded from further analysis. One exclusion involved a patient undergoing SKPT retransplantation; the other three exclusions were patients receiving Simulect induction as part of a prospective trial comparing ALI *versus* no ALI therapy. The remaining 28 patients underwent primary SKPT with PE drainage and no antibody induction and make up the study group.

### Organ Procurement, Preservation, and Preparation

The pancreas and/or kidney was procured from heart-beating cadaveric donors in conjunction with multiple-organ retrieval using standardized techniques.<sup>8</sup> University of Wisconsin (UW) solution was used for both *in situ* flush and storage of all organs under cold-storage conditions. Whole-organ pancreaticoduodenosplenectomy was performed using an *en bloc* technique.<sup>8</sup> Cold ischemia was kept to a minimum, and pancreas preservation times were <20 hours in all cases and <12 hours in 10 (36%) of cases.<sup>9</sup> Before transplantation, the pancreas was reconstructed on the back table with a donor iliac artery bifurcation Y graft to the splenic and superior mesenteric arteries.<sup>10</sup> The PE procedure requires that the arterial bifurcation graft be constructed intentionally long for subsequent arterialization. The portal vein was mobilized and dissected back to the splenic and superior mesenteric venous confluence without the need for a venous extension graft. The proximal duodenal staple line (just distal to the pylorus) was inverted with suture, and the distal duodenal closure incorporated the third and a variable length of the fourth portion of the duodenum, as previously described.<sup>4,5</sup> The closure of the mesenteric root was reinforced with a running suture. The spleen was left attached to the tail of the pancreas to be used as a handle, but in some cases the splenic hilar structures were ligated in continuity before revascularization. The kidney was likewise prepared using standard techniques. The kidney and pancreaticoduodenal grafts were repackaged separately in sterile fashion in cold UW solution before implantation.

### Recipient Selection and Surgical Procedure

Patients were selected for SKPT based on ABO blood type compatibility, degree of sensitization, period of time on the waiting list, a negative T-lymphocytotoxic crossmatch, medical urgency, and human leukocyte antigen matching, in

accordance with United Network for Organ Sharing guidelines.

After preparation of the organs, the recipient procedure is performed through a midline intraperitoneal approach. The renal allograft is anastomosed end-to-side to the left iliac vessels, followed by an extravesical ureteroneocystostomy using standard techniques. The kidney is then “retroperitonealized” by anchoring the sigmoid colon mesentery to the lateral peritoneal reflection with interrupted sutures.

The surgical technique of PE drainage has been previously described in detail by our group.<sup>4,5</sup> The portal vein of the pancreas graft is anastomosed end-to-side to a major tributary of the superior mesenteric vein. The donor iliac artery bifurcation graft is brought through a window made in the distal ileal mesentery and anastomosed end-to-side to the right common iliac artery. The transplanted duodenum is anastomosed distally end-to-end to a diverting Roux-en-Y limb of recipient jejunum. Splenectomy is performed after revascularization, and an attempt is made to anchor the tail of the pancreas to the anterior abdominal wall with interrupted sutures. These anchoring sutures permit subsequent percutaneous, ultrasound-guided pancreas allograft biopsies to be performed as needed.<sup>11</sup>

A nasogastric tube, central venous line, and urethral catheter are placed at the beginning of the surgical procedure, and two closed-suction drains are placed medial and lateral to the pancreas allograft at the end of the procedure before wound closure.

## Perioperative Management and Immunosuppression

Preoperative antibiotic prophylaxis consisted of a preoperative dose, an intraoperative dose, and three postoperative doses of cefazolin (1 g intravenous). All patients received single-strength sulfamethoxazole/trimethoprim 1 tablet/day for 6 to 12 months as prophylaxis for *Pneumocystis* pneumonia. Antifungal prophylaxis consisted of oral fluconazole 200 mg/day for 2 to 3 months.<sup>12</sup> Antiviral prophylaxis included intravenous ganciclovir (2.5 to 5 mg/kg twice daily) during the initial hospital stay, followed by oral ganciclovir (1 g three times daily) for 3 months (for 6 months if the donor was seropositive for cytomegalovirus [CMV] and the recipient was seronegative).<sup>13</sup>

All patients undergoing SKPT received primary immunosuppression with tacrolimus, MMF, and steroids without ALI therapy. The first nine patients received intravenous tacrolimus (starting dose 1 mg/day) as a continuous infusion to ensure early therapeutic levels. Subsequently, the practice was changed, and the last 19 patients received oral tacrolimus starting on postoperative day 1 at a dose of 0.1 to 0.2 mg/kg orally in two divided doses. Tacrolimus dosing was titrated to a 12-hour trough level of 15 to 25 ng/ml by IMX assay for the first 3 months. After 3 months, tacrolimus blood levels were maintained at 10 to 15 ng/ml. Oral MMF was begun immediately after the transplant at 2- to 3 g/day

in two to four divided doses. The MMF dose was reduced in patients with gastrointestinal intolerance (nausea, vomiting, diarrhea) or when the total white blood cell count was  $<3000/\text{mm}^3$ . MMF was discontinued temporarily in patients with active CMV infection or septicemia, or when the total white blood cell count was  $<2000/\text{mm}^3$ ; it was restarted later at a reduced dose. Corticosteroids were administered as intravenous methylprednisolone 500 to 1000 mg during surgery, followed by 250 mg on postoperative day 1, and then tapered to 30 mg/day oral prednisone by day 7 to 10. A gradual steroid taper was used, aiming at an oral prednisone dose of 5 to 10 mg/day at 1 year.

Patients were monitored in the intensive care unit for 24 to 36 hours before being transferred to the transplant unit. Nasogastric tube decompression was maintained for 2 to 3 days, closed-suction drainage for 3 to 5 days, and urethral catheter drainage for 5 to 7 days. Antiplatelet therapy consisting of oral aspirin (81 mg/day) was administered to all patients. In addition, 3000 to 5000 units of intravenous heparin was administered as a single dose during surgery before implantation of the pancreas. In selected cases, heparin prophylaxis was continued after surgery (5000 units subcutaneously twice daily) for 3 to 5 days. Oral coumadin in a single dose of 1 mg/day was administered to patients requiring prolonged vascular access or those with subsequent placement of a permanent central venous catheter.

## Postoperative Monitoring

After transplantation, duplex ultrasonography of the pancreas and kidney was performed on the first postoperative day and whenever clinically indicated. Recipients were serially monitored for daily fasting serum glucose, amylase, and lipase levels, renal profiles, tacrolimus levels, and complete blood cell counts. Metabolic control and hormonal profiles were assessed by intravenous glucose tolerance testing, fasting and stimulated C-peptide levels, lipid profiles, and glycosylated hemoglobin levels.<sup>14</sup> The diagnosis of rejection was based on clinical criteria, renal allograft dysfunction, serum amylase and lipase levels, serum glucose levels, a change in the slope of glucose disappearance, and renal or pancreas allograft histopathology.<sup>14–16</sup> Renal allograft rejection was suggested by an unexplained rise in serum creatinine of 0.3 mg/dl or greater and confirmed by ultrasound-guided percutaneous biopsy.<sup>11</sup> Pancreas allograft rejection was suggested by an unexplained elevation in serum amylase, lipase, or glucose and confirmed by ultrasound-guided percutaneous biopsy. The severity of rejection was defined according to the Banff criteria in kidney biopsies<sup>17</sup> and by a modification of the Maryland classification of allograft rejection in pancreas biopsies.<sup>18</sup>

Mild renal allograft rejection was treated with intravenous methylprednisolone 500 to 1000 mg/day for three doses. Antilymphocyte therapy with OKT3 or ATGAM for 7 to 10 days was used as the initial treatment for moderate or severe renal allograft rejection or for any pancreas allo-

**Table 1. GROUP CHARACTERISTICS**

Number	28
Age (years)	38.4 (26–54)
Gender	
Female	13 (46%)
Male	15 (54%)
Race	
White	26 (93%)
Black	2 (7%)
Years of diabetes	25.1 (9–35)
Total insulin dose (units/day)	42.5 (15–72)
Prior kidney transplant	4 (14%)
Pretransplant dialysis	
None	11 (39%)
Hemodialysis	8 (29%)
Peritoneal dialysis	9 (32%)
Duration of dialysis (months)	15.2 (6–27)
Waiting time (months)	4.0 (0.25–10)
Current PRA $\geq$ 10%	4 (14%)
HLA	
ABDr match	1.55 (0–5)
ABDr mismatch	4.1 (1–6)
Cold ischemia (hours)	
Pancreas	12.9 (6–18)
Kidney	13.3 (7–21)
Donor (D)/Recipient (R) CMV serologic status	
D+/R–	3 (11%)
D+/R+	11 (39%)
D–/R+	3 (11%)
D–/R–	7 (25%)
Unknown	4 (14%)

PRA, panel reactive antibody titer.

graft rejection. Steroid-resistant mild renal allograft rejection was also treated with antilymphocyte therapy.

CMV infection was defined as a positive blood culture, antigenemia, or positive IgM titer. Invasive CMV infection (CMV disease) was defined as symptomatic CMV infection or histologic evidence of tissue invasion. Treatment of CMV infection consisted of intravenous ganciclovir for 2 to 4 weeks and a reduction in immunosuppression. Oral ganciclovir was given for a variable period after treatment of a documented CMV infection. Other infections were recorded, with major infection defined as the need for hospital admission for diagnosis and treatment.

## Statistical Analysis

Data are reported as mean and range. Renal allograft loss was defined as a return to dialysis or to the pretransplant serum creatinine level. Pancreas graft loss was defined as the need for continuous insulin therapy.

## RESULTS

A total of 28 primary SKPTs with PE drainage were performed without ALI during the 26-month study. Demographic, immunologic, and transplant characteristics of the

study group are listed in Table 1. The study group included 15 men and 13 women with a mean age of 38 years and a mean pretransplant duration of diabetes of 25 years. Twenty-six patients were white and two were black. The mean pretransplant total insulin dose was 42.5 units/day. Four patients had undergone prior kidney transplantation. At the time of SKPT, 11 patients were not yet on dialysis; the remaining 17 (8 hemodialysis, 9 peritoneal dialysis) had a mean pre-SKPT duration of dialysis of 15 months.

Four patients had a current panel reactive antibody titer of  $\geq 10\%$  at the time of transplant. The mean human leukocyte antigen match was 1.5, and the mean mismatch was 4.1. The mean cold ischemia times for the pancreas and kidney were 12.9 hours and 13.3 hours, respectively. Three patients were at risk for primary CMV exposure (donor CMV seropositive and recipient CMV seronegative); in seven cases both the donor and recipient were CMV seronegative.

Results are depicted in Table 2. Actual patient, kidney, and pancreas graft survival rates were 86%, 82% and 82%, respectively, after a mean follow-up of 1 year. All renal allografts had immediate graft function. Four patients died, three as a result of cardiac events at 1, 7, and 14 months after SKPT. In each of these cases, the cardiac event was unrelated to the SKPT. The fourth death occurred in a patient with severe orthostatic hypotension that resulted in pancreas allograft thrombosis at 2 weeks and hepatic hypoperfusion with liver failure, resulting in death at 2 months. Two of the four deaths occurred in patients with previous pancreas graft loss. All of the deaths were believed to be related to preexisting autonomic neuropathy, affecting either cardiac or circulatory reflexes. If the three cardiac deaths were censored, patient, kidney, and pancreas graft survival rates were 96%, 92%, and 88%, respectively.

Five renal allografts were lost, including three deaths

**Table 2. RESULTS (N = 28)**

Patient survival	24 (86%)
Graft survival: Kidney	23 (82%)
Pancreas	23 (82%)
Follow-up (months)	12.1 (1–26)
Dialysis posttransplant	0
Initial hospitalization: length of stay	12.5 (6–30)
Total charges	\$99,517 (\$75,146–\$141,634)
Number of readmissions	2.9 (0–8)
No readmissions	10 (36%)
Acute rejection	9 in 6 (21%)
Chronic rejection	3 in 2 (7%)
Major infection	13 in 9 (32%)
CMV infection	3
Line sepsis	3
Urosepsis	2
Intraabdominal infection	2
Other infection	3
Urinary tract infection	4 (14%)
Relaparotomy	7 (25%)
Multiple reoperations	3 (11%)
Prolonged vascular access	9 (32%)

with functioning grafts at 1, 2, and 7 months. The other renal graft losses resulted from chronic rejection at 13 months and viral nephritis at 15 months. In addition, there were five pancreas graft losses, including two deaths with functioning grafts at 1 and 7 months. Two other pancreas grafts were lost as a result of chronic rejection, both at 13 months. The remaining pancreas graft loss resulted from severe orthostatic hypotension and thrombosis, as noted above. In the patient who died at 14 months from a cardiac event, both the kidney and pancreas grafts had been lost as a result of chronic rejection 1 month earlier.

A total of six patients (21%) had acute rejection, and five (18%) received antilymphocyte therapy. Four patients had one episode of rejection (two kidney, two pancreas), with two receiving ATGAM, one OKT3, and one steroid therapy alone. Another patient had two episodes of rejection (one kidney, one kidney-pancreas) and received steroids and then OKT3; however, the pancreas graft was subsequently lost to chronic rejection at 13 months. The remaining patient had three episodes of rejection (one kidney, two kidney-pancreas) and received two courses of OKT3 and one course of ATGAM before losing both grafts to chronic rejection at 13 months. There was no graft loss resulting from acute rejection.

The mean length of stay and total charges for the initial hospital stay were 12.5 days and \$99,517. Nine patients (32%) were dismissed within 8 days of SKPT. The mean number of readmissions was 2.9, and 10 patients (36%) had no readmissions. Seven patients (25%) underwent relaparotomy, including two for allograft pancreatectomy, one for splenic artery thrombectomy, and one for pancreatitis and evacuation of hematoma. The remaining three patients underwent multiple reoperations. One patient underwent laparotomy for bleeding and then a second procedure for peritonitis. Another patient underwent repair of a wound dehiscence and then a second (negative) laparotomy for rejection. The remaining patient underwent three procedures for a superior mesenteric artery thrombectomy, a second-look procedure, and then drainage of a peripancreatic abscess. The mean number of laparotomies per patient was 0.4. In two patients (7%) intraabdominal infection developed; each was treated with surgical exploration and drainage. There were no deaths or graft losses as a result of either surgical complications or pancreatitis.

A total of 13 major infections occurred in nine patients (32%). There were three cases each of CMV infection and line sepsis, two cases each of urosepsis and intraabdominal infection, and one case each of bacterial esophagitis, ehrlichiosis, and polyoma viral interstitial nephritis involving the renal allograft. The latter infection was the only cause for graft loss. In four patients, urinary tract infections developed. Dehydration with the need for intravenous fluid supplementation and placement of long-term indwelling central venous catheters occurred in nine cases (32%). There were no deaths or pancreas graft losses from infection. Of the 24

surviving patients, 22 (92%) are both dialysis- and insulin-free.

## DISCUSSION

This series demonstrates the initial results associated with combining the technique of PE pancreas transplantation and newer immunosuppression management strategies that eliminate the need for ALI. The role of ALI induction has been debated extensively in the kidney transplantation literature but has been accepted routinely in SKPT because of the high rejection rates seen in these patients.<sup>7,19</sup> Our results indicate that in the context of PE transplantation and tacrolimus/MMF-based therapy, excellent graft survival and exceedingly low rejection rates can be achieved in SKPT.

The history of clinical pancreas transplantation largely revolves around the development and application of various surgical techniques. Bladder drainage by the duodenal segment technique became popular because it is safe, sterile, and convenient, enables urinary monitoring of pancreatic secretions, affords access for cystoscopic biopsy, and permits easy control of anastomotic problems with urethral catheter drainage.<sup>20</sup> However, this technique creates a non-physiologic connection between the allograft pancreas with duodenal conduit and the urinary bladder, resulting in obligatory fluid and bicarbonate losses in the urine as well as alterations in the normally acidic enzyme-free milieu of the lower genitourinary tract.<sup>3</sup> Although well tolerated in many pancreas transplant recipients, bladder drainage has been associated with unique metabolic and urologic complications resulting from altered physiology. When these complications become intractable, conversion from bladder to enteric drainage (enteric conversion) may be therapeutic.<sup>3</sup> Enteric conversion rates range from 10% to 20% in most large series.<sup>21</sup>

Because of a favorable experience with enteric conversion, coupled with advances in preservation and immunosuppression that placed the duodenal segment at a lower risk for ischemic or immunologic injury, a resurgence of interest has occurred in primary enteric drainage in an effort to avoid the complications of bladder drainage.<sup>7,20,21</sup> In the United States, the number of pancreas transplants performed with enteric drainage has increased from 15% in 1995 to 33% in 1996 to 46% in 1997.<sup>1</sup> The majority of transplants with enteric drainage are performed with systemic venous delivery of insulin (systemic-enteric). At present, most pancreas transplants are performed with either systemic-bladder or systemic-enteric drainage. According to the latest registry report analyzing transplants performed between Jan. 1, 1994, and June 1, 1998, the 1-year pancreas graft survival rates with bladder and enteric drainage were 83% and 81%, respectively ( $p \leq 0.05$ ).<sup>1</sup> The slight improvement in graft survival associated with bladder drainage is almost entirely accounted for by the slightly lower technical failure rate associated with this technique. In patients with primary enteric drainage, however, Roux limb diversion

was also associated with a slight improvement in graft survival as a result of a lower technical failure rate.

A few centers have reported success transplanting the pancreas to a mesenteric vein of the recipient to reestablish portal venous drainage of insulin. This technique can be performed with enteric drainage (PE) to improve the physiology of the transplant procedure. A recent survey of pancreas transplant centers revealed that 39 perform bladder drainage, 21 both bladder and enteric drainage, and 18 enteric drainage exclusively.<sup>22</sup> Seven centers reported experience with the PE technique; five of these use a diverting Roux limb. The PE technique, first described clinically by our group in 1992,<sup>23</sup> was based on experimental work by Shokouh-Amiri et al in a porcine model.<sup>24</sup> This new technique employed a tributary of the superior mesenteric vein to reestablish portal venous drainage and differed substantially from the original reports of portal pancreatic transplants (Calne in 1984,<sup>25</sup> Muhlbacher et al in 1990,<sup>26</sup> and Rosenlof et al in 1992<sup>27</sup>).

In 1993, our group reported that PE pancreas transplantation with Roux limb diversion not only achieves acceptable metabolic control and eliminates hyperinsulinemia, but is also associated with a reduced incidence of postoperative complications.<sup>2</sup> In 1995, we compared 19 patients undergoing SKPT with the PE technique with a retrospective control group of 28 patients undergoing SKPT with the conventional systemic-bladder technique.<sup>5</sup> Actual patient and graft survival rates at 1 and 3 years were no different in the two groups. Metabolic and urologic complications and urinary tract infections were more common in the systemic-bladder group. Metabolic control was comparable between groups, and peripheral hyperinsulinemia did not occur in patients with PE drainage.

In 1997, Nymann et al from our group reported improving outcomes with increased experience with the PE technique.<sup>28</sup> Two groups were compared: 23 SKPTs with PE drainage performed from 1991 to 1994 versus 23 PE pancreas transplants performed from 1995 to 1996. The latter group received tacrolimus-based immunosuppression; the former group received cyclosporine. Cold ischemia time and perioperative blood transfusions were significantly less in the latter group. In addition, the incidence of technical graft loss was reduced from 26% to 9%. Consequently, 1-year patient and pancreas graft survival rates were improved in the most recent era. In a subsequent study, Nymann analyzed 47 SKPTs with graft function at 1 month, including 30 with systemic-bladder drainage and 17 with PE drainage.<sup>15</sup> All patients had received cyclosporine-based therapy. The authors noted comparable patient and graft survival and surgical complication rates but demonstrated that the incidence of rejection, the incidence of graft loss from rejection, and the density of rejection were all less in patients with PE drainage. These reduced rejection rates in the PE patients formed the basis for our attempt to eliminate induction therapy from the regimen.

Paralleling our efforts with PE transplantation was the

development of two new immunosuppressive agents, tacrolimus and MMF. The safety and efficacy of these two agents led to the extension of their use in the SKPT population. Preliminary experience with tacrolimus induction, maintenance, and rescue therapy after pancreas transplantation has been promising, as was a similar experience with MMF.<sup>7</sup> Subsequently, a number of single-center reports and one multicenter study reported favorable experience with the simultaneous use of tacrolimus and MMF in pancreas transplant recipients.<sup>7,29-32</sup> In most of these cases, however, recipients received ALI in combination with tacrolimus and MMF. With these new agents, the incidence of acute rejection after SKPT has ranged from 10% to 40%.

In 1998, Corry et al<sup>33</sup> reported successful pancreas transplantation without ALI therapy in 123 consecutive patients, including 104 SKPTs. Also in 1998, Burke et al<sup>34</sup> reported a low rate of acute rejection in nine consecutive pancreas transplants (eight SKPT) managed with tacrolimus, MMF, and steroids without ALI. In each of these reported experiences, however, the technique of transplantation was either systemic-bladder or systemic-enteric.

We believe that the present study represents the first prospective analysis of SKPT with PE drainage in patients not receiving ALI therapy. The study demonstrated that only one fifth of the patients had rejection episodes, and that 67% of those were single rejection episodes that responded to initial therapy. Overall, the elimination of induction therapy resulted in reduced hospital costs and earlier hospital dismissal, as evidenced by the fact that nearly one third of the patients were discharged within 8 days of transplantation.

The one problem encountered in this series is the rate of death with functioning grafts. Three of the four deaths resulted from cardiac events unrelated to SKPT. These deaths accounted for 5 (3 renal, 2 pancreas) of the 10 graft losses that occurred in this study and were related to pre-existing cardiac disease with autonomic neuropathy. We have previously identified cardiac autonomic neuropathy as a risk factor for sudden death in patients with sustained autonomic dysfunction after pancreas transplant.<sup>35</sup> The occurrence of these deaths, however, has prompted us to further our efforts into autonomic system monitoring. If these three deaths are excluded, the remaining 25 had a censored patient survival rate of 96% and kidney and pancreas graft survival rates of 92% and 88%, respectively; this compares quite favorably with both single-center and registry data.

Considering that the incidence of acute rejection was 21%, 82% of patients were spared exposure to antilymphocyte therapy. There was no renal or pancreas graft loss as a result of acute rejection; however, one renal and two pancreas graft losses occurred as a result of chronic rejection, each at 13 months after SKPT. Further, despite the administration of tacrolimus immediately after SKPT to achieve early therapeutic levels, there were no cases of delayed renal allograft function, and no patient required dialysis after

transplant. Whether portal delivery of antigen conferred an immunologic advantage above and beyond that achieved with the new immunosuppressants remains to be determined.<sup>15</sup>

In the absence of ALI, the intensive care unit stay was considerably shortened, and tolerability of the new drug regimen was much improved. By avoiding exposure to antilymphocyte agents, the posttransplant course was much less complicated from a medical standpoint, hospital charges were less, and the length of stay was reduced. In the absence of bladder drainage, metabolic acidosis was rare, and dehydration resulting in the need for prolonged vascular access with intravenous fluid supplementation occurred in less than one third of cases with PE drainage. We have identified dehydration as a common cause of readmission after pancreas transplant, regardless of technique. Many of these patients have severe gastroparesis, enteropathy, and autonomic neuropathy with symptomatic orthostatic hypotension. For these reasons, we have a low threshold for placing central venous catheters for intermediate-term (1 to 3 months) vascular access for either intravenous fluid or medication administration.

Despite recent advances, surgical complications remain an important source of morbidity after pancreas transplants.<sup>21,36</sup> With increased experience with the PE technique, we have previously reported a decrease in the relaparotomy rate from 45% to 29%.<sup>37</sup> In addition, the mean number of relaparotomies per patient decreased from 1.2 to 0.5. In the present series, our relaparotomy rate was 25%, with a mean of 0.4 procedures per patient. There were no deaths or grafts lost in this series as a result of surgical complications. The one pancreas graft loss as a result of thrombosis (3.6%) occurred 2 weeks after SKPT in the setting of severe orthostatic hypotension resulting in shock. The reported surgical complication rate after pancreas transplantation with bladder drainage ranges from 24% to 36%.<sup>20,21,36–43</sup> According to United Network for Organ Sharing registry data, the pancreas graft thrombosis rate after SKPT is 5%.<sup>44</sup> Therefore, SKPT with PE drainage can be performed with a surgical complication and thrombosis rate similar to that of other techniques of pancreas transplantation.

In the recent past, the disadvantages of primary enteric drainage included the inability to monitor exocrine secretions directly, septic complications (*e.g.*, peritonitis, abscess, mycotic aneurysm), and healing problems related to performing an anastomosis between an ischemic organ to inadequately prepared bowel in the setting of high-dose immunosuppression with incomplete distal decompression.<sup>21</sup> With either systemic-bladder or systemic-enteric drainage, the reported incidence of intraabdominal infection ranges from 13% to 33%.<sup>20,21,45–50</sup> In the present series, we noted two cases (7%) of intraabdominal infection, both resulting in relaparotomy. We believe that Roux limb diversion may confer protection of the enteric anastomosis, and the absence of exposure to antilymphocyte agents may

result in a reduced risk of infection. The overall rate of major infection in this study was 32%, with only three cases of CMV infection (11%). Although we noted a marked reduction in urinary tract infections, we did note some unusual opportunistic infections, including one case of ehrlichiosis and another case of viral interstitial nephritis, possibly from a polyoma virus. All patients received prophylaxis with ganciclovir, fluconazole, and sulfamethoxazole/trimethoprim.<sup>12,13</sup> We did not find any cases of ganciclovir-resistant CMV infection or infection with Epstein-Barr virus, *Pneumocystis*, or fungi. Although the majority of patients did not receive antilymphocyte therapy, we continue to administer targeted antiinfective prophylaxis because of the presumed risk of opportunistic infections in the setting of more intense maintenance immunosuppression with the newer agents. In this series, there was no death or pancreas graft loss as a result of infection.

In summary, these preliminary results suggest that SKPT with PE drainage and immunosuppression with tacrolimus, MMF, and prednisone without ALI can be performed with results comparable to other pancreas transplantation techniques with ALI. We noted a low incidence of metabolic and urologic complications without incurring excessive risk for surgical or infectious complications. In addition, we noted a low immunologic risk without impairment in allograft function. Studies with more patients and longer follow-up are needed to document the beneficial effects of portal venous delivery of insulin on carbohydrate and lipid metabolism. However, because of its physiologic, economic, and immunologic advantages, SKPT with PE drainage and no ALI may soon become the standard of care in pancreas transplantation.

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## Discussion

DR. JOHN C. McDONALD (Shreveport, Louisiana): This is a detailed report on the current outcome of simultaneous kidney-pancreas transplantation, and is another fine presentation from the Memphis group. . . (which) has led the field in reestablishing the concept that best results are obtained when endocrine activity is delivered through the portal system and exocrine function through the GI tract. This concept was thought correct intuitively in the early efforts of transplanting the pancreas but was soon abandoned because of technical complications.

I would like to ask what is the secret which has led to the reduction in technical complications? I suspect it is the development of better techniques of organ retrieval. Would the essayists discuss this point? In any event, I became convinced about 2 years ago that this was the proper way to perform this operation. Dr. Gaber graciously received a couple of my associates in Memphis and took them through that procedure a couple of times, and it was adopted in our clinic with good results.

Insofar as the deletion of the antilymphocyte induction therapy is concerned, I recognize the appeal of the cost reduction by deleting this agent; however, insofar as I know, efforts to delete induction therapy in other situations have always resulted in increased incidents of acute rejection soon after transplantation. This is true in our clinic, certainly, with kidney allografts, since we have studied that point.

I think the question of deleting induction therapy in this situation will need to be settled in a randomized trial, because these data show that you can get good results without it, but it does not show that you cannot get better results with it. So I wonder if you plan such a trial.

Finally, I would like to draw your attention to the fact that in this series of 28 kidney pancreas transplants with portal venous drainage of the pancreas, only two kidneys were lost due to rejection, a failure rate of about 7%, and this outcome is substantially better than that nationally with kidney transplants alone.

There is substantial literature on the tolerogenic effect of antigens presented to the host through the portal system. Would you comment upon this observation? Do you think portal drainage is responsible, and if so, could you suggest a mechanism?

DR. MARK H. DEIERHOI (Birmingham, Alabama): I believe that one of the problems which has limited the dissemination of this form of therapy for diabetics has been the technical difficulties associated with the pancreas and problems related to technical complications and other side effects. And the results demonstrated by the Memphis group certainly give us encouragement that it is possible to perform this operation with a similar morbidity and similar outcomes to kidney transplantation alone.

I have three questions for them related to the conduct of their combined kidney-pancreas transplantation in their program.

First of all, given the increasing incidence of diabetic renal failure and the increased number of juvenile diabetics with renal failure presenting to most programs, the progressive increase in the length of waiting lists, and knowing how poorly juvenile diabetics do with long-term dialysis, do you have specific selection criteria for identifying patients for the combined operation, both in relation to living donor transplantation and cadaveric transplantation? In other words, do you offer this operation as a primary procedure to all juvenile diabetics? Or is your selection determined to any extent by the availability of a living donor for the patient?

I would like to also echo Dr. McDonald's comments regarding the decrease in acute rejection and its relationship to portal drainage, and in relationship to the use of antilymphocyte agents, and ask whether you feel there is any place for the use of the newer anti-IL-2 receptor antibodies which do not have some of the side effect and administration problems associated with older antilymphocyte agents?

DR. DANIEL H. HAYES (Charlotte, North Carolina): The name of this paper is what first caught my eye. When you think about the overview of transplantation in general with pancreas transplantation in its evolution, you can almost equate this to the maturation of your child. Heart transplants, kidney transplants, and liver transplants are our children as they have entered and finished college. Lung and pancreas are in their adolescence, and intestinal transplants are our infants.

And for those of you not associated with transplantation in general, I'd like to take just a moment to put things in perspective. There are over 40,000 people awaiting kidney transplants in the United States, about 11,000 awaiting liver transplants, 4000 awaiting heart transplants, 3000 lungs, and 1000 pancreas, with about 400 awaiting intestinal transplants. And on an annual basis in the United States, there are about 12,000 kidneys, 4000 livers, 3000 hearts, 1000 pancreas, and about 900 lungs. So you can see that from the standpoint of pancreas transplantation, we are truly in an evolution.

As John Ochsner taught us in our residency in New Orleans many years ago, when an operation has so many applications and ways that it can be done, you should probably look at the underlying premise for the operation. Pancreas transplantation is purely and simply a surgical treatment for Type I diabetes. And if we think about applying whole-organ pancreas transplantation with transplanting about half of the duodenum, when we are looking really for the islets of Langerhans which contain the insulin produced in beta cells, those cells, those islets comprise about 2% of the pancreas. So the next evolution, hopefully, of pancreas transplantation will be islet transplantation, which will eliminate about 98% of the tissue that we transplant which causes 100% of the complications of this procedure.

What we have heard from our new member, Dr. Gaber, this morning, as has been stated previously, is an excellent presentation. Dr. Gaber is really the pioneer of portal drainage of the pancreas blood flow and has shown very clearly that histologically—or biochemically, rather—this portal drainage makes a profound effect on the hyperinsulinemic state.

My first question for Dr. Stratta, even though he is a new member of the group, will be: as Dr. Gaber has been doing this procedure since the early 1990s, have you seen any clinical outcomes and effects of reducing atherosclerotic disease in your recipients as a result of the portal drainage of the pancreas?

The second question relates to the enteric drainage. I think we all would agree that enteric drainage of the exocrine pancreatic function is reasonable. It never made any sense that we should plug this into the bladder. You have a 30% incidence of dehydration with this procedure into the gut, which is essentially the same incidence as bladder-drained exocrine pancreatic function. Why is there essentially the same incidence of dehydration in the two procedures?

Next, I'd like just to get your thoughts, if you would, Dr. Stratta, on induction therapy. Dr. Deierhoi and Dr. McDonald both asked about induction therapy. And in this case, the manuscript is very,

very clear. Dr. Gaber says he is not using induction therapy with antilymphocyte preparations. And I agree with that completely; however, I do feel that you are using induction therapy with tacrolimus. Shooting for levels of 15 to 20 in the early posttransplant period is, in fact, I think induction therapy, and I'd like to hear your thoughts and comments on that.

Lastly, you had one patient that rejected both organs at 14 months, and a patient that had acute rejection early—one of the few patients that did reject early. Did you have trouble attaining adequate tacrolimus levels in that patient early on? And do you have a protocol for a contingency of adding antilymphocyte therapy in patients in whom you cannot achieve adequate blood levels of drug early posttransplant if their GI tract is just not absorbing it or for other reasons? At what point do you feel like an inadequate level dictates further therapy?

Lastly, I'd like to compliment Dr. Louis Britt. He is the author, if you will, of the Memphis transplant program. He is responsible for the wealth of personnel, including Dr. Gaber and Dr. Stratta, who present this material to us. If you look at the success of this program over the past few years, you will realize that the pancreas program, particularly at Memphis, has become an internationally acclaimed program, and I think that we are lucky as an Association to have them in our membership.

DR. GAZI B. ZIBARI (Shreveport, Louisiana): Great progress has been made in the development of glucose testing and insulin delivery system since Dr. Banting and Dr. Best first discovered insulin. These methods are still only treatments for diabetes and not a cure. Pancreatic transplantation, when successful, offers the real hope of a cure for diabetes. Between 1966 and 1987, some 1300 pancreas transplantations were performed worldwide. Between 1987 to 1995, some 5500 pancreatic transplantations were done. Of these, about 4200 were done in North America.

There are five reasons for the increase in pancreatic transplantation over the last decade. That includes an improved immunosuppression, improvement in donor management and preservation solution, improvement of infection management, progress in anesthesia and ICU care and, finally, improvement in surgical techniques.

The portal enteric drainage technique was first described by this group in 1992. Dr. Gaber and Dr. Britt were kind enough to invite us to go to Memphis to observe their technique of combined kidney and pancreas transplantation. Since that time, we have adopted their technique of portal enteric drainage and use of a diverting Roux-en-Y limb.

Since that time, we have done a total of 12 combined kidney and pancreas transplantations. We have used OKT3 for induction therapy in addition to Neoral, Cellcept, and prednisone. Although our experience is limited, we have 100% patient and graft survival, and only 10% of our patients suffered an acute rejection which responded to steroids. It did not require any further antibody therapy.

With this in mind, I have several questions I would like the authors to discuss:

One, what was the PRA and number of antigen match on graft lost to rejection?

Two, four of 28 patients died, three of which were due to cardiac events. Can you tell us what was the previous cardiac evaluation?

Three, you have reported 0% incidence of delayed graft function or ATN, low cold ischemic time, and only 2 of 28 patients were African American. Do you think if you have to transplant more

African Americans and have a higher incidence of delayed graft function, this might cause more acute rejection?

Finally, I agree with the authors that we need a larger prospective randomized clinical trial to answer this important question about induction therapy.

DR. ARNOLD G. DIETHELM (Birmingham, Alabama): Dr. Clyde Barker in the middle 1960s wrote a paper in the *Annals of Surgery* regarding portal enteric drainage in dogs and, in a relatively small series, found that it made no difference in terms of antigen processing by the liver and improvement of graft survival. That was a long time ago and, of course, that may change today.

The second comment is what kind of markers are you going to use to determine whether portal enteric drainage is better than bladder drainage or systemic drainage and hyperinsulinemia? It is difficult to know. One could say graft survival would be one. Patient survival is another, but how are you going to determine whether hyperinsulinemia is a negative component of the "standard" kidney-pancreas transplant procedure?

Lastly, you think back about antilymphocyte induction, and it was really used, at least the quadruple therapy, was popularized Dr. Belzer and Dr. Deierhoi at Wisconsin, and it was a method to allow a period of time for ATN to recover in the transplanted kidney.

We were concerned at that time that cyclosporine would cause nephrotoxicity, and nephrotoxicity on top of a kidney with tubular injury would then be a problem. If you use short-term ischemia with kidneys, you don't need induction therapy. We have not used induction therapy as routine therapy for some time if the kidney has prompt function.

We start cyclosporine in 24 hours or shortly thereafter with all our living related donors. That may have something to do with why the liver people have had such good results with early transplantation and certainly, the heart people, because they have an excellent kidney, can start immediately with either tacrolimus or cyclosporine. But I would be particularly interested how you are going to assess the outcome of these two comparable procedures in determining that one is better than the other in selecting a marker other than morbidity and mortality?

DR. ROBERT J. STRATTA (Closing Discussion): When I arrived in Memphis. . . there were two overriding principles in my pancreas transplant experience: one was the technique of systemic bladder drainage and the other being quadruple immunosuppression with antilymphocyte induction. And when I arrived, I was somewhat horrified to see that neither of these caveats were being followed. Certainly, one of attractions to Memphis was to learn this new technique of portal enteric transplantation, which in some circles is still regarded as heretical, but I was quickly convinced. We did perform a prospective trial in 1997 comparing systemic bladder with portal enteric drainage, and we are currently in the process of performing a prospective trial with systemic enteric *versus* portal enteric drainage. With those thoughts in mind, I would like to answer some of the questions.

With regard to Dr. McDonald, there is a decrease in surgical complications after pancreas transplantation, regardless of technique, across the board at the present time. I believe the reduction in risk is multifactorial. I agree with you that some of that is related to improvements in retrieval, certainly improvements in preservation. I think keeping cold ischemia to a minimum is certainly very relevant, similar to the liver experience when the UW solution

came out and we thought that we could extend preservation up to about 20 hours with the liver, but now the standard of care is to keep liver preservation below 12 hours.

My initial experience is I was willing to go out to about 24 hours with pancreas preservation, but Dr. Gaber correctly retaught me that if we can keep that cold ischemia to 12 hours or less, I think it pays some dividends in terms of less preservation-related pancreatitis and, therefore, a lower surgical complication rate.

In addition, the advances in immunosuppression have clearly led to a reduction in the rate of rejection. And rejection can sometimes present as pancreatitis or a duodenal segment perforation, which is one of the Achilles' heels of pancreas transplantation.

In addition, I think donor selection is critical in terms of reducing the surgical complication rate. And, fortunately, in our area of the country we still have the luxury of being fairly selective in our donor population for the kidney-pancreas recipient.

Regarding deleting antibody induction in kidney-pancreas transplantation—and this also relates to the comments of Dr. Diethelm—kidney-pancreas patients are different than kidney patients. And although I would agree that if one can get immediate renal allograft function, one does not need antibody induction as an immunosuppressive umbrella to cover the recipient.

There is no question that kidney-pancreas patients reject more than kidney-alone patients. They are a high immunologic risk by definition. Whether that is related to diabetes being an autoimmune disorder, and they have an activated immune system, or whether it is related to a double transplant as opposed to a single transplant, no one has been able to quite work out. But in the recent past, when rejection rates with cadaver kidney transplantation were in the 40% to 60% range, all of the centers with kidney-pancreas were reporting rejection rates of 60% to 80%. And this is as recent as 3 or 4 years ago.

So that performing kidney-pancreas without induction therapy is clearly a leap of faith, but we have been able to accomplish that, I believe, not so much with the portal delivery of antigen but more with the new immunosuppressants. And I would agree with the comment that we are doing induction, but we are doing induction with tacrolimus as opposed to an antibody induction agent.

I think our low rate of graft loss is related more to the improvements in immunosuppression than to the reduction in cold ischemia. In this series, a third of the patients had cold ischemia of less than 12 hours, and all of them were below 18 hours. And I would agree that if you can shorten cold ischemia or improve preservation with machine preservation as opposed to cold storage preservation, one can get immediate function. It's a lot easier then to manage the immunosuppression and reduce the rate of rejection.

With regard to Dr. Deierhoi, I would agree that the decision for the young uremic diabetic comes down to one between living related kidney transplantation *versus* kidney-pancreas transplantation. And if one is in an area where waiting times are excessive, or particularly if the patient is referred late and they have already been on dialysis for a year or more, I think certainly the priority would be to render them dialysis-free ahead of insulin-free. And that's particularly true if they have a willing, living donor, and especially if that living donor is a 6-antigen match for that particular recipient.

Fortunately or unfortunately, many times we can't find living donors for our patients. But when we report the various results and outcomes of the different types of transplants available for the uremic diabetic, more times than not they opt for the kidney-

pancreas if the waiting time is not going to be excessive and they are not highly sensitized.

We currently are part of a multicenter randomized trial looking at the issue of induction *versus* no induction. Some of those centers in that trial are using some of the new monoclonals as their induction agent, as are we. And others are using more of the traditional agents. So I would agree that this issue of induction *versus* no induction in kidney-pancreas transplantation needs to be answered by a randomized multicenter study, which is currently ongoing.

I appreciate the comments of Dr. Hayes. And in my brief experience at the University of Tennessee with the portal venous delivery technique, I have not really seen any difference in macrovascular complications. But I think a lot of that is recipient selection because, unfortunately, we are still seeing patients late and we are transplanting them too late. It's pretty hard to reverse blindness or a heart attack or an amputation when the patient presents to you with any or all of those.

With regard to enteric *versus* bladder drainage, in our experience, 100% of the patients have dehydration and metabolic acidosis with bladder drainage. They are all on bicarbonate, and many require prolonged vascular access. In this series, about one third of our portal enteric patients had Hickman lines placed for management, not so much for dehydration—we call it dehydration, but it is more for orthostatic hypotension and autonomic neuropathy.

We are a referral center for autonomic neuropathy, and many of these patients are debilitated by autonomic neuropathy. And we find that early on, if we send them home with IV fluids and with IV medications if they are not able to tolerate the oral forms, we find that they are a little easier to manage short-term.

Again, with the issue of antilymphocyte induction, if you are not using induction, I think it is critical to get high FK levels early after transplant. And I rarely, if ever, have seen an early acute rejection with induction therapy, but that can happen when one is not using the monoclonal or polyclonal agents for induction. So that we will use IV tacrolimus in those cases if the patient is not able to tolerate the oral form early after transplant, particularly when they have an NG tube still in place. So our contingency for that is to switch the IV form of the medications.

With regard to Dr. Zibari, in our patients who did experience rejection, all of them had 0% PRA, and all of them were a zero match, which is consistent with our series where these patients have a low degree of match and, for the most part, are 0% PRA. We did not note in those particular patients that we had difficulty achieving high FK levels early after transplant.

I think the major negative of this study was the four deaths, because pancreas and kidney transplantation, unlike liver and heart transplantation, are considered life-enhancing rather than life-saving organ transplants. And I think having any mortality in kidney or pancreas patients is completely unacceptable.

But when one looks at the survival of uremic diabetics on dialysis and, in particular, the uremic diabetic that has severe autonomic neuropathy, I think one could make a case that this procedure is rapidly becoming a life-saving rather than a life-enhancing operation.

Of the four deaths, three were cardiac, and all of them were due to sudden death, which we believe was related to sustained autonomic dysfunction after the transplant. These were patients that were at home with functioning grafts who were suddenly found dead. They did not have any history of a heart attack, any history of structural coronary artery disease.

Our cardiac evaluation, similar to what President Griffen mentioned, is to examine the patient, talk to the patient, find out how functional they are, do an EKG, an echo, a stress thallium, and if any of those tests are positive, then to refer them to a cardiologist for a cardiac catheterization; in our experience, about one third of the patients have cardiac catheterization. It is very disturbing to have three cardiac deaths in this small experience, but I think it is really related to the patient population that is being referred to us because of the interest that we have in autonomic neuropathy. And I think in the future we are prospectively evaluating these patients pre- and posttransplant for autonomic neuropathy, particularly related to cardiac and circulatory reflexes. And we may be able to define a risk group that may not benefit from transplantation.

With regard to 2 of the 28 patients being African American, Type I diabetes in African Americans is unusual. In our kidney experience, about 50% of our patients are African American, but in our kidney-pancreas experience, it is very unusual to find an African American that has Type I diabetes and renal failure as well. We are beginning to extend the kidney-pancreas transplan-

tation now to Type II insulin-requiring diabetics, so we do forecast that in the future we will be performing more kidney-pancreas transplants on African Americans. We do consider African Americans at a little higher immunologic risk than Caucasians, and whether or not we can achieve similar results in terms of low-rate rejection is largely unknown.

I think it is really important to keep the cold ischemia to a minimum—you asked about donor selection—and particularly if one is using a less-than-ideal donor, to keep that ischemia less than 12 hours.

I appreciate Dr. Diethelm's comments. We really can't say whether hyperinsulinemia in this population causes problems long-term, but I can tell you in terms of patients being referred to you, the endocrinologists who control those patients, they are the gatekeepers. And when they hear you are doing an operation that results in hyperinsulinemia, they get very nervous, and they are unwilling to refer patients to you. But when you are doing a much more physiologic procedure, which results in physiologic delivery of insulin, they are much more interested in the technique.